7. The method of claim 1, wherein said effector comprises a reporter gene selected from the group consisting of chloramphenicol acetyl transferase (CAT), luciferase, beta -galactosidase (β-gal), alkaline phosphatase, horse radish peroxidase (HRP), growth hormone (GH), and green fluorescent protein (GFP).

10. The method of claim 1, wherein said ligand and metabolic product respectively are selected from the group consisting of beta-catenin and a Tcf, a NF-κB and I-κB, a P53 and MDM2, a receptor and its receptor partner.

Please add the following new claim 94:

--94. The method of claim 1, wherein said metabolic product is a metabolic product that is accumulated by said cell.--

These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position. In accordance with the requirements of 37 C.F.R. § 1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

REMARKS

Status of the Claims.

Claims 1-21 and 94 are pending and under consideration with entry of this amendment, claims 22-93 being withdrawn from consideration pursuant to a restriction requirement made final, and claim 94 being added herein. Claims 1, 7, 10, and 19 are amended herein. The amendments provided herein do not alter the scope of the claims and introduce no new matter. Support is replete throughout the specification (*see, e.g.*, the claims as filed).

Election/Restriction.

Pursuant to a restriction requirement made final, Applicants cancel claims22-93 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent

applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Drawings.

Applicants note that the drawings were objected to because the writing in Figure 1 was allegedly difficult to read. Applicants have submitted a substitute drawing with entry of this amendment thereby obviating this objection.

35 U.S.C. §112, Second Paragraph.

Claims 7, 10, 19, and 21 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because:

A) There was allegedly insufficient antecedent basis for the limitation "said reporter gene" in line 1 of claim 7;

B) The phrase "heteromelic receptor partner" recited in claim 10, was allegedly not a term of art

C) The role of the "second nucleic acid" in claim 21 was allegedly unclear; and

D) The phrase "a nucleic acid" in claim 19 was allegedly unclear.

Claim 7 is amended herein to clarify that the effector recited in claim 1 is a reporter gene recited in claim 7. This amendment provides adequate antecedent basis thereby obviating the Examiner's rejection.

Claim 10 was amended herein to eliminate the term heteromelic thereby obviating the rejection of this claim.

With respect to claim 21, claim 1 is amended herein to recite a "**first** nucleic acid" thereby distinguishing that nucleic acid from the "second nucleic acid" recited in claim 21, and thereby obviating the rejection of claim 21.

With respect to the §112, second paragraph rejection of claim 19, the Examiner is respectfully reminded that a claim is definite if:

> [R]ead in light of the specification [it] reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits. [emphasis added] *Hybritech Inc. v*

> *Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81 (Fed. Cir. 1986) cert. denied 480 U.S. 947 (1987).

In the instant case, the invention contemplate embodiments a nucleic acid encoding the first or said second chimeric protein is the same as the nucleic acid encoding a peptide binding site and an effector gene, as well as embodiments where different nucleic acids encode the first or said second chimeric protein and the encoding a peptide binding site and an effector gene. Claim 19 is intended to read on both embodiments. The nucleic acid recited there can therefore be either the same as the nuclei acid recited in claim 1 or a different nucleic acid. A plain reading of the claim language clearly admits both possibilities. Accordingly, the claim apprises those of skill in the art of the utilization and scope of the invention, and the language is as precise as the subject matter permits. Claim 19 thus meets the requirements of 35 U.S.C. §112, second paragraph, and the rejection of claim 19 on these grounds should be withdrawn.

Applicants note that the foregoing amendments do not narrow the scope of the amended claims. Accordingly, upon issuance of these claims, Applicants are to be afforded a full scope of the Doctrine of Equivalents (*see, e.g., Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, No. 00-1543, (S. Ct. 2002)).

35 U.S.C. §102.

Claims 1, 2, 6, and 10-12 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Karin *et al.* (U.S. Patent 6,242,253). Applicants respectfully traverse.

The Examiner is respectfully reminded that anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." *Kalman v Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983).

In the instant case, claims 1-21 are directed to a method of screening for an agent that "modulates the ability of a cell **to accumulate or to degrade a metabolic product**". Claim 1 expressly recites:

> (iii) detecting an alteration of expression of said effector gene wherein a difference in the expression of said effector gene in said test cell, as compared to a control cell contacted with a lower concentration of test agent or no test agent **indicates that said test agent modulates the ability of said cell to accumulate or degrade said metabolic product.** [emphasis added]

The cited art fails to teach, suggest, or otherwise disclose the use of a two-hybrid system to screen for an agent that alters the ability of a cell to accumulate or degrade a metabolic product. To the contrary, Karin *et al.* teaches the use of a two hybrid system **to screen agents that alter the association** of two proteins (an IKK subunit and a protein know to bind the IKK). Thus, for example, Karin states:

> A screening assay of the invention provides a means to identify an agent that **alters the association** of an IKK complex or an IKK catalytic subunit with a second protein such as the regulatory subunits discussed above. As used herein, the term modulate" or "alter" when used in reference to the association of an IKK and a second protein means that **the affinity of the association is increased or decreased** with respect to a steady state, control level of association, i.e., in the absence of an agent. [emphasis added] (col 21, lines 31-39)
>
> * * *
>
> [A]transcription activation assay such as the yeast two-hybrid system also **is useful as a screening assay to identify agents that alter association** of an IKK subunit and a second protein known to bind the IKK. [emphasis added] (col 25, lines 43-46)

Karin *et al.* thus focuses on the use of a two hybrid system to screen for agents that modulate the association/affinity of IKK and another protein. Karin *et al.* **fails to disclose** the use of a two hybrid system to screen for agents that modulate the ability of a cell to accumulate or degrade a metabolic product. Karin *et al.* thus fails to anticipate the present invention and the rejection of claims 1, 2, 6, and 10-12 were rejected under 35 U.S.C. §102(e) should be withdrawn.

35 U.S.C. §103(a).

Claims 1-12, and 19-21 were rejected were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Karin *et al.* as applied to claims 1, 2, 6, and 10-12, further in view of Sadowski *et al.* (U.S. Patent 5,885,779), Young (1998) Biology of Reproduction, 58: 302-311, and Finley *et al.* (1997) Pp. 197-214 In: The Yeast Two-Hybrid System, P Partel, and S. Fields, Oxford University Press. Claims 1-21 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of

Barker *et al. (U.S. patent 5,851,775), in view of Sadowski et al.*, Young (1998), Finley *et al.*, Nagahara *et al.* (1998) Nature Medicine, 4: 1449-1452, and Schwarze *et al.* (1999) Science, 285: 12569-1572. The Examiner alleged that Karin *et al.* teaches the use of a two hybrid assay to screen for agents that alter the association of IκB kinase with a second protein such as IκB or a regulatory protein. Young was cited as allegedly teaching the use of a repressor protein, VP16, Gal4, or Gal4Y, reporter genes such as β-galactosidase, an apoptosis gene or cytotoxin. Finley *et al.* was cited as teaching the use of inducible promoters and Sadowski *et al.* was cited as allegedly teaching the use of a transcriptional repressor domain rather than a transactivation domain. Barker *et al.* was cited as allegedly teaching using a two hybrid assay to screen for compound s that inhibit the biding of β-catenen and Tcf-4. Nagahara *et al.* and Schwarze *et al.* were cited as allegedly teaching the use of an HIV TAT domain to promote internalization of proteins or other molecules. Applicants respectfully traverse.

A *prima facie* case of obviousness requires that the combination of the cited art, taken with general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Geiger*, 815 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection, the cited references must additionally provide a reasonable expectation of success. *In re Vaeck,* 20 USPQ2d 1438 (Fed. Cir. 1991), citing *In re Dow Chemical* Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). In the instant case, the cited art fails to teach or suggest the use of a two hybrid system to screening for an agent that modulates the ability of a cell to accumulate or to degrade a metabolic product.

As explained above, the presently pending claims are directed to a method of screening for an agent that modulates the ability of a cell **to accumulate or to degrade a metabolic product.**

In contrast, the cited references utilize the two-hybrid system to evaluate protein-protein interactions or to screen for agents that alter protein-protein interactions, **not to screen for agents that modulate the accumulation or degradation of a metabolic product**.

Thus, Karin *et al.*, as described above, teaches the use of a two-hybrid system **to screen agents that alter the association** of two proteins (an IKK subunit and a protein know to bind the IKK). Thus, for example, Karin states:

> A screening assay of the invention provides a means to identify an agent that **alters the association** of an IKK complex or an IKK catalytic subunit with a

> second protein such as the regulatory subunits discussed above. As used herein, the term modulate" or "alter" when used in reference to the association of an IKK and a second protein means that **the affinity of the association is increased or decreased** with respect to a steady state, control level of association, i.e., in the absence of an agent. [emphasis added] (col 21, lines 31-39)

Similarly, Sadowski *et al* teaches the use of a "repressed transactivator system for characterization of protein-protein interactions":

> The invention provides **a system for assaying protein-protein interactions**. [emphasis added] (abstract)
>
> * * *
>
> The RTA system of the invention can also be employed for use in identifying and characterizing **specific compounds that inhibit protein-protein interactions**. In the RTA system, inhibitors of a specific protein-protein interaction will interfere with recruitment of the repressor function of the prey fusion protein, resulting in activation of reporter gene expression. [emphasis added] (col 5, lines 38-40)

Sadowski *et al.* simply offers no teaching or suggestion of a screening system for an agent that modulates the ability of a cell **to accumulate or to degrade a metabolic product.** The claimed invention is therefore simply not obvious in light of the combination of Karin *et al.* and Sadowski *et al.*

This defect is not remedied by the remaining cited references. Both Young and Finley teach the yeast two-hybrid system as a system for screening for protein-protein interactions, not as a system for screening for modulators of the ability of a cell to accumulate or to degrade a metabolic product:

> The yeast two-hybrid method is a powerful technique for analyzing these **protein-protein interactions**. . . . Additionally, two-hybrid techniques provide a rapid and versatile system for the further characterization of discrete **protein-protein** interactions. [emphasis added] (Young, abstract)
>
> * * *

> Protein-protein interactions as therapeutic targets using two-hybrid methodologies avail specific design for drug discovery research. [emphasis added] (Young, pp308, col 2 through pp 309, col 1).

> Larger scale two hybrid approaches typically rely on interaction mating. In this method the protein fused to the activation domain (here called the prey) are expressed in two different haploid yeast strains of opposite mating type (MATa and MATalpha), and **the strains are mated to determine if the two proteins interact**. Mating occurs when haploid yeast strains of opposite mating type come into contact, and results in fusion of the two haploids to form a diploid yeast strain. Thus, **an interaction can be determined** by measuring activation of a two-hybrid reporter gene in the diploid strain. [emphasis added] (Finley *et al.* page 1)

Again, there is simply no teaching or suggestion of screening for modulators of the ability of a cell to accumulate or to degrade a metabolic product.

As recognized by the Examiner, Barker *et al.* teaches the use of a two hybrid assay to screen for compounds that inhibit the binding of β-catenin and Tcf-4. There is no teaching or suggestion of screening for modulators of the ability of a cell to accumulate or to degrade a metabolic product.

Nagahara *et al.* and Schwarze *et al.* pertain to the use of a human immunodeficiency virus TAT protein to transduce proteins into target cells. These references offer no teaching or suggestion whatsoever of a two hybrid system or of methods of screening for modulators of the ability of a cell to accumulate or to degrade a metabolic product.

The combination of the cited art simply fails to teach or suggest the presently claimed invention. Accordingly, the rejection of claims 1-21 under 35 U.S.C. §103(a) should be withdrawn.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN 09/687,593 WITH ENTRY OF THIS AMENDMENT

In the specification:

Replacement of Figure 1.

Page 32, lines 7-15:

Where it is desired to recombinantly express either of the two chimeric molecules comprising the two-hybrid systems of this invention[~~, the G250, the GM-CSF, or the G250-GM-CSF fusion protein,~~] the nucleic acid sequences encoding the desired protein are typically operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements typically include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants may additionally be incorporated.

In the claims:

1. A method of screening for an agent that modulates the ability of a cell to accumulate or to degrade a metabolic product, said method comprising:

(i) providing a mammalian cell comprising:

a **first** nucleic acid encoding a peptide binding site and an effector gene;

a first chimeric protein comprising a nucleic acid binding domain that binds said peptide binding site attached to said metabolic product or to a ligand that binds to said metabolic product; and

a second chimeric protein comprising an expression control protein attached to said metabolic product or to said ligand that binds to said metabolic product such that when said first chimeric protein comprises said metabolic product, said second chimeric protein comprises

said ligand and when said first chimeric protein comprises said ligand, said second chimeric protein comprises said metabolic product;

(ii) contacting said cell with a test agent; and

(iii) detecting an alteration of expression of said effector gene wherein a difference in the expression of said effector gene in said test cell, as compared to a control cell contacted with a lower concentration of test agent or no test agent indicates that said test agent modulates the ability of said cell to accumulate or degrade said metabolic product.

7. The method of claim 1, wherein said **effector comprises a** reporter gene **[~~is~~]** selected from the group consisting of chloramphenicol acetyl transferase (CAT), luciferase, **[b]beta** galactosidase (**[b]β**-gal), alkaline phosphatase, horse radish peroxidase (HRP), growth hormone (GH), and green fluorescent protein (GFP).

10. The method of claim 1, wherein said ligand and metabolic product respectively are selected from the group consisting of beta-catenin and a Tcf, a NF-κB and I-κB, a P53 and MDM2, a receptor and its **[~~heteromelic~~]** receptor partner.

94. (New) The method of claim 1, wherein said metabolic product is a metabolic product that is accumulated by said cell.

APPENDIX B

CLAIMS PENDING IN USSN 09/687,593 WITH ENTRY OF THIS AMENDMENT

1. A method of screening for an agent that modulates the ability of a cell to accumulate or to degrade a metabolic product, said method comprising:

(i) providing a mammalian cell comprising:

a first nucleic acid encoding a peptide binding site and an effector gene;

a first chimeric protein comprising a nucleic acid binding domain that binds said peptide binding site attached to said metabolic product or to a ligand that binds to said metabolic product; and

a second chimeric protein comprising an expression control protein attached to said metabolic product or to said ligand that binds to said metabolic product such that when said first chimeric protein comprises said metabolic product, said second chimeric protein comprises said ligand and when said first chimeric protein comprises said ligand, said second chimeric protein comprises said metabolic product;

(ii) contacting said cell with a test agent; and

(iii) detecting an alteration of expression of said effector gene wherein a difference in the expression of said effector gene in said test cell, as compared to a control cell contacted with a lower concentration of test agent or no test agent indicates that said test agent modulates the ability of said cell to accumulate or degrade said metabolic product.

2. The method of claim 1, wherein said expression control protein is a transactivator.

3. The method of claim 2, wherein said transactivator is VP16.

4. The method of claim 1, wherein said expression control protein is a repressor.

5. The method of claim 1, wherein said nucleic acid binding protein is selected from the group consisting of GAL-4, and GAL-4-Y.

6. The method of claim 1, wherein said effector is selected from the group consisting of a reporter gene, a cytotoxin, and an apoptosis gene.

7. The method of claim 1, wherein said effector comprises a reporter gene selected from the group consisting of chloramphenicol acetyl transferase (CAT), luciferase, beta -galactosidase (β-gal), alkaline phosphatase, horse radish peroxidase (HRP), growth hormone (GH), and green fluorescent protein (GFP).

8. The method of claim 1, wherein said effector encodes a cytotoxin selected from the group consisting of thymidine kinase, pseudomonas exotoxin, diphtheria toxin, ricin, and abrin.

9. The method of claim 1, wherein said apoptosis gene is selected from the group consisting of P53, P73, Bax, Bad, FADD, and a caspase.

10. The method of claim 1, wherein said ligand and metabolic product respectively are selected from the group consisting of beta-catenin and a Tcf, a NF-κB and I-κB, a P53 and MDM2, a receptor and its receptor partner.

11. The method of claim 1, wherein said first chimeric protein is expressed from a nucleic acid in said cell.

12. The method of claim 1, wherein said second chimeric protein is expressed from a nucleic acid in said cell.

13. The method of claim 1, wherein said first chimeric protein is a protein transported into said cell.

14. The method of claim 1, wherein said first chimeric protein is a protein transported into said cell.

15. The method of claim 1, wherein said first chimeric protein or said second chimeric protein comprises an HIV TAT domain.

16. The method of claim 1, wherein said cell is a cell selected from the group consisting of SW480, SW48, DLD-1, HCT-116, HT29, 293, U-20S, T-47D, MCF-7, HeLa, A549, Hep G2, and a Jarkat cell.

17. The method of claim 1, wherein

said nucleic acid encodes a GAL-4 binding site, and said effector gene is a reporter gene;

said first chimeric protein comprises a GAL-4 nucleic acid binding protein and a beta catenin or a Tcf;

said second chimeric protein comprises a VP-16 and beta catenin or a Tcf.

18. The method of claim 17, wherein said Tcf is Tcf4.

19. The method of claim 1, wherein said cell comprises a nucleic acid encoding said first or said second chimeric protein under control of a tissue specific or an inducible promoter.

20. The method of claim 19, wherein said promoter is an ecdysone promoter.

21. The method of claim 1, wherein said cell further comprises a second nucleic acid encoding said ligand or metabolic product operably linked to an inducible promoter.

94. The method of claim 1, wherein said metabolic product is a metabolic product that is accumulated by said cell.